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(57) Abstract

A method of treating stress in a patient showing stress related symptoms is disclosed, where the method comprises administering to the patient an effective amount serotoninergic drugs. Specific examples of this class of drugs are described, and include as examples, among others, the use of lithium, chlorimipramine, fluoxetine, fluvoxamine, sertraline, MK-212, Ro 60-0332/ORG 35035, Ro 60-175/ORG 35030, d,l-fenfluramine, dexfenfluramine, or their salts.

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COMPOSITION FOR TREATMENT OF STRESS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The invention relates to a novel process for treating stress in a subject suffering from at least one symptom of stress. More specifically, the invention relates to the use of drugs which enhance serotonin-mediated neurotransmission such as fenfluramines for treating stress in such a subject.

DESCRIPTION OF THE RELATED ART

At present, patients suffering from stress related disorders are treated for their symptoms of stress by the use of pharmaceutical compositions containing drugs such as anxiolytics or sometimes with beta-blockers. Anxiolytics frequently used include drugs such as benzodiazepines, diazepam being a specific example. The beta-blocking drugs used for treatment of such patients include propranolol. The use of these classes of drugs for such treatments is discussed in *Goodman and Gilman's Pharmacological Basis of Therapeutics,* Seventh Edition, 1985, Alfred G. Gilman et al., editors, pages 192-201, incorporated by reference.

Stress is classified by convention as being either acute or chronic in nature. A patient suffering from a stress related disorder may exhibit a variety of types of symptoms. These symptoms can include anxiety, depression, and overeating. The conventional treatment for a patient suffering from a stress related disorder is by use of drugs such as the benzodiazepines or by use of beta-blocking drugs such as propranolol. Disclosed here is a novel treatment method for stress in a patient, which method uses drugs hitherto unknown as useful for treating stress. The novel method disclosed herein provides a useful method for treating patients suffering from stress and exhibiting at least one symptom thereof. In a specific embodiment of the invention, said method has been found particularly useful for treating the stress felt by subjects who also suffer from overeating disorders or who overeat in reaction to the stress that they are experiencing.

It should be noted here that not all patients who overeat would benefit from a treatment for alleviating stress. Some people who overeat respond to stress by reducing their eating, not increasing their eating behavior. Drugs that reduce the effects of stress in a patient might not necessarily be useful in all obese patients. In the present invention, the stress reducing drugs that prove to be the most useful are those that elicit in patients, whose overeating is stress associated, a response that leads to a reduction in their eating behavior. Hence, not all stressed people who overeat would be candidates for the treatment with drugs that enhance serotonin-mediated neurotransmission of the invention.

A number of compounds are known to stimulate or enhance serotonin-mediated neurotransmission and are sometimes referred to as serotoninergic drugs. These compounds include the following: d,l-fenfluramine, dexfenfluramine, tryptophan, lithium, chlorimipramine,

cyanimipramine, fluoxetine, paroxetine, fluvoxamine, citalopram, femoxitine, cianopramine, sertraline, sibutramine, venlafaxine, ORG 6582, RU 25591, LM 5008, DU 24565, indalpine, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone, amitriptyline, imipramine, trimipramine, doxepin, protriptyline, nortriptyline, dibenzoxazepine, deprenyl, isocarboxazide, phenelzine, tranylcypromine, furazolidone, procarbazine, moclobemide, brofaromin, nefazodone, bupropion, MK 212, DOI, m-CPP, Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, α-methyl-5-HT, TFMPP, bufotenin, Ru 24969, quipazine, 5-carboxyamidotryptamine, sumatriptan, CGS 12066, 8-OH-DPAT, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, SB 206553, and pharmaceutically acceptable salts thereof. Suitable salts can be formed from the above compounds, for example, as addition salts using the following acids: the hydrohalic acids, sulfuric acid, phosphoric acid or an organic acid such as acetic acid, maleic acid, valeric acid, caproic acid, benzoic acid or nicotine acid.

By "fenfluramines" here is meant a racemic mixture of d,l-fenfluramine, which is also called N-ethyl-α-methyl-3-(trifluoro-methyl)benzeneethanamine; the dextrorotatory isomer known as dexfenfluramine and also as d-fenfluramine; or the pharmaceutically acceptable salts of these compounds. Suitable salts can be formed from dexfenfluramine or d,l-fenfluramine, for example, as addition salts using the following acids: the hydrohalic acids, sulfuric acid, phosphoric acid or an organic acid such as acetic acid, maleic acid, valeric acid, caproic acid, benzoic acid or nicotinic acid.

For practicing the invention, the active serotonin-mediated neurotransmission stimulating compound may be administered to a patient as a pharmaceutical composition comprising the active compound admixed with a pharmaceutically acceptable carrier, including one or more excipients. For example,

fenfluramines may be administered to a patient as a pharmaceutical composition comprising either dexfenfluramine or d,l-fenfluramine admixed with a pharmaceutically acceptable carrier, including one or more excipients.

The serotoninergic drugs MK-212, DOI, m-CPP, Ro 60-0175/ORG 35030 , Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, and SB 206553 fall into the class of drugs which activate postsynaptic receptors. These are agonist drugs which bombard the serotonin receptors of postsynaptic cells and mimic the effect of large amounts of serotonin reacting with the postsynaptic cells' serotonin receptors.

For the purposes of this disclosure, the terms "subject" and "patient" may be used interchangeably to refer to a human exhibiting at least one symptom of stress.

The pharmaceutically acceptable carrier and/or excipient of choice utilized for a formulation

used in accordance with the invention depends on the mode of administration to a subject. The compositions of this invention are suitable for parenteral, buccal, sublingual or rectal administration. The resulting pharmaceutical compositions are, for example, tablets, coated tablets, capsules, soft gelatin capsules, drinkable emulsions, suspensions or solutions for oral or injectable administration, sublingual tablets or suppositories. They may also be formulated into a sustained release form. Among the various excipients which may be used for these purposes include talc, magnesium phosphate, lactose or silica or the like. To the solid forms may be added a filler, a diluent, a binder such as ethyl-cellulose, dihydroxypropyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, gum arabic, gum tragacanth or gelatin. The compositions of this invention may also be flavored, colored or coated with a wax or a plasticizer. It is to be understood that those skilled in the art of pharmaceutical formulation will be able to make a variety of formulations that would be within the scope of this disclosure and the appended claims, without departing from the spirit and teachings of the invention. It is intended that all such formulations be included in this invention.

It is to be understood that according to the teachings of the invention, the invention may be practiced by administering serotonin-mediated neurotransmission stimulating compounds, for example, fenfluramines, to a subject as a single unit dose one or more times per day, or as a plurality of unit doses once or more times per day without deviating from the teachings of the invention.

Other drugs, preferably halogenated amphetamines, may also be useful to treat stress in a subject who is suffering from the kind of stress alleviated by the fenfluramine treatments of the present invention. Such other useful drugs may include specific drugs that are not halogenated amphetamines including, but not limited to, effexor, nefazodone, bupropion, paroxetine, fluoxetine, and sertralin.

Dexfenfluramine and d,l-fenfluramine are known anorectic agents as disclosed in U.S. Patent No. 3,198,834. However, prior to the present invention, neither serotoninergic drugs in general, nor dexfenfluramine nor d,l-fenfluramine has been known to be effective as a treatment for stress in a patient.

Fenfluramines are known to be effective drugs for treating obesity. The racemic mixture, d,l-fenfluramine, was disclosed in U.S. Patent 4,452,815, granted to Wurtman and Wurtman, as being effective for inhibiting the abnormal craving for carbohydrates which afflicts some people and which is associated with their obesity. Dexfenfluramine is also indicated for use in treating patients who cannot control their eating habits or appetite. The use of dexfenfluramine for this purpose was disclosed in U.S. Patent 4,309,445. In both of these patents the use proposed for fenfluramines was for treating a patient's appetite or craving for certain types of food. Nowhere in these patents is the use of fenfluramines suggested for treatment of the stress from which a patient may be suffering.

A theoretical mechanism by which fenfluramines work for suppressing appetite for certain food types was presented by Wurtman and Wurtman in Brain Serotonin, Carbohydrate-Craving,

Obesity and Depression, *Obesity Research,* vol. 3, suppl. 4, November 4, 1995, pages 477S-480S incorporated by reference. It has been prop sed that dexfenfluramine is an effective treatment for the overeating that is associated with a response to stress in some people. People overeat for a variety of reasons, however. For some people their overeating seems to be a response to stressful situations. Dexfenfluramine is shown in this publication to be useful for treating the obesity suffered by such people, but there is no teaching that dexfenfluramine is useful for treating stress itself.

Fenfluramines are serotoninergic drugs that inhibit the abnormal craving for high carbohydrate foods, which leads to a positive caloric balance and subsequent obesity in certain people. Some, but not all, people benefit from the administration of dexfenfluramine by having their craving for certain foods inhibited. This above cited publication does not disclose or teach any use of dexfenfluramine or d,l-fenfluramines for treating stress itself in obese patients, or make any suggestion that these fenfluramines may be effective as a treatment for stress itself. The publication describes the serotoninergic fenfluramines as acting to facilitate weight loss in subjects in three ways:

> "They accelerate the onset of satiety and enhance basal metabolic rate by about 100 calories per day. They also inhibit the 'carbohydrate craving' manifested by many people who are overweight or are becoming so, and there is reason to believe that this inappropriate eating behavior actually constitutes a 'serotonin hunger' by the brain, in which case giving the serotoninergic drug might constitute a specific therapy for the etiologic process causing the obesity."

Further discussion of the known functioning of fenfluramines is found in Wurtman and Wurtman, Brain Serotonin, Carbohydrate-Craving, Obesity and Depression, *Recent Advances in Tryptophan Research,* G. A. Filippini et al. eds., Plenum Press, New York, 1996, pages 35-41 incorporated by reference.

The use of dexfenflurarnine for treating animals inflicted with periodic pain is discussed in Dexfenfluramine: Effects on Food Intake in Various Animal Models, Neil E. Rowland and Janis Carlton, *Clinical Neuropharmacology,* vol 11, suppl. 1, pp. S33-S50 incorporated by reference. This article indicates in its abstract that: "...both stress-induced eating as well as a food-motivated response (running) are particularly sensitive to inhibition by dexfenfluramine."

This article discloses the administration of dexfenfluramine to rats exhibiting increased eating behavior in response to tail pinching. The tails of the rats were pinched as part of an experimental protocol, which was found to cause the rats to eat larger amounts of food than rats whose tails were not pinched. Dexfenfluramine (DF) was found to decrease the eating behavior of the tail pinched rats. Dexfenfluramine was known prior to the Rowland et al. article to depress eating activity, however, as shown in Wurtman et al., *Science,* vol. 198, pp. 1178-1180, December, 1977 incorporated by reference.

The authors discussed the implications of their experiments with regard to stress-induced eating as follows on page S37 (DF indicating dexfenfluramine):

"Mild tail pressure induces eating and gnawing in rats, and this may be a model of stress-induced eating in humans. Garattini reported that DF potently inhibits tail pressure-induced eating, and that the DI_{50} of 0.6 mg/kg is about one-half of the doses effective in the other paradigms reviewed so far. It was previously reported that racemic fenfluramine inhibits tail pressure-induced eating as well as concurrent behaviors such as gnawing, locomotion, and vocalization. In the study with DF, only the amount eaten was reported, rather than all oral behaviors. These data thus suggest that DF may be an especially potent inhibitor of stress-related eating. Further studies are needed to clarify the effect of DF on other oral behaviors, as well as whether it has 'antistress' effects along with its anorectic action."

Thus, until the present invention, it was only known that dexfenfluramine inhibits eating in tail pinched rats. It was not previously known that serotoninergic drugs, for example dexfenfluramine or d,l-fenfluramine could be an effective treatment for stress. The authors of this article indicated only that fenfluramines inhibit tail pinching-induced eating and other behaviors stemming from the tail pinching protocol. They did not disclose that the fenfluramines could be used as treatments for reducing stress itself. Thus, Rowland et al. had no idea dexfenfluramine would exhibit any stress relieving activity per se. Indeed, it is doubtful that tail pinching and the consequent behavior from the rat induced by the tail pinching could serve as a meaningful, let alone reliable, model for the types of stress experienced by humans.

The applicants' experiments have now permitted the discovery that such antistress effects can be achieved with serotoninergic drugs in general and fenfluramines in particular.

On page S37 of Rowland it is noted that the tail pinched rats "may be a model of stress-induced eating in humans", but no indication is provided therein that the rat system was in fact an accepted model of stress-induced eating in humans. Since the rat system was not a valid model for human behavior, one skilled in the art would not have been led by the results of Rowland with rats, to treat humans suffering from stress with dexfenfluramine.

SUMMARY OF THE INVENTION

Briefly, the present invention is a novel treatment for stress and symptoms of stress in a subject. The applicants have discovered that administering Page 7, line 18. Administering serotoninergic drugs in general and fenfluramines in particular to a patient can bring about a reduction in the stress felt by patient and the symptoms of stress manifested by the patient. The treatment of stress and stress related symptoms of a patient with these compounds has not been reported previously.

The present invention provides an appropriate treatment for stress in human patients,

especially those suffering from stress-induced overeating. This invention is based on the discovery that the serotoninergic drugs, for example fenfluramines, such as d,l-fenfluramine, dexfenfluramine, or their salts can alleviate symptoms of stress in patients, when administered in effective amounts or at appropriate dosages.

Accordingly, the present invention is directed to a method of treating a human subject exhibiting one or more symptoms of stress, which comprises administering to the subject an effective amount of a compound which enhances serotonin-mediated neurotransmission such as d,l-fenfluramine or dexfenfluramine, or a pharmaceutically acceptable salt thereof. In a specific embodiment of the invention, when the fenfluramine is d,l-fenfluramine or a pharmaceutically acceptable salt thereof, an effective dose ranges from about 15 to about 150 mg/day, preferably from about 40 to about 80 mg/day. When the fenfluramine is dexfenfluramine or a pharmaceutically acceptable salt thereof, an effective dose ranges from about 5 to about 150 mg/day, preferably from about 15 to about 45 mg/day.

According to the present invention, a treatment is provided which results in a reduction in the stress level of the patient experiencing emotional and other kinds of stress.

Accordingly, it is an object of the invention to provide a treatment for stress perceived by a stress-induced overeating patient.

It is another object of the invention to provide a treatment for stress which is also useful for controlling food intake in a stress-induced overeating patient.

It is another object of the invention to provide a treatment for non-eating-related stress symptoms of a patient.

It is another object of the invention to provide a treatment for stress in a patient, wherein the treatment is with a drug other than an anxiolytic or beta-blocking drug.

Other objects will become apparent from the description of the invention which follows.

DETAILED DESCRIPTION OF THE INVENTION

We have discovered a novel method for treating stress, said method comprising the administration of stimulators of serotonin-mediated neurotransmission such as fenfluramines to a patient with stress related symptoms. In one preferred embodiment, the method comprises the administration of effective amounts of either d,l-fenfluramine, dexfenfluramine, or their salts. Other preferred embodiments provide detailed disclosure of the use of other compounds which enhance serotonin-mediated neurotransmission.

A number of compounds are shown to enhance serotonin-mediated neurotransmission, and thus to be useful in treating humans with one or more symptoms of stress. These compounds include

the following: d,l-fenfluramine, dexfenfluramine, tryptophan, lithium, chlorimipramine, cyanimipramine, fluoxetine, paroxetine, fluvoxamine, citalopram, femoxitine, cianopramine, sertraline, sibutramine, venlafaxine, ORG 6582, RU 25591, LM 5008, DU 24565, indalpine, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone, amitriptyline, imipramine, trimipramine, doxepin, protriptyline, nortriptyline, dibenzoxazepine, deprenyl, isocarboxazide, phenelzine, tranylcypromine, furazolidone, procarbazine, moclobemide, brofaromine, nefazodone, bupropion, MK-212, DOI, m- CPP, Ro 60-0175/ORG 35030, and Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, α-methyl-5-HT, TFMPP, bufotenin, Ru 24969, quipazine, 5-carboxyamidotryptamine, sumatriptan, CGS 12066, 8-OH-DPAT, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, SB 206553, and pharmaceutically acceptable salts thereof.

The serotoninergic drugs MK-212, DOI, m-CPP, Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, and SB 206553 fall into the class of drugs which activate postsynaptic receptors. These are agonist drugs which bombard the serotonin receptors of postsynaptic cells and mimic the effect of large amounts of serotonin reacting with the postsynaptic cells' serotonin receptors. Examples of the use of three of these drugs along with the chemical names and sources are shown in EXAMPLES 13-15.

6-Chloro-2-(1-piperazinyl)pyrazine (MK-212), is obtained from Merck & Co., Inc. Whitehouse Station, NJ. (S)-2-(4, 4, 7-trimethyl-1, 4-dihydro-indeno (1, 2-B) pyrrol-1-yl-1-methylethylamine (Ro 60-175/ORG 35030) is obtained from F. Hoffmann-LaRoche Ltd., Basel, Switzerland. (S)-2-(Chloro-5-fluoro-indol-1-yl)-1-methylethylamine (Ro 60-0332/ORG 35035) is obtained from F. Hoffmann LaRoche Ltd., Basel, Switzerland. 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) is obtained from Research Biochemical International, Natick, MA. 1-(3-Chlorophenyl)piperazine (m-CPP) is obtained from Research Biochemical International, Natick, MA.

It is to be understood that the present invention as disclosed herein, also includes a method of making a medicament for treating stress, wherein the method comprises a step of mixing dexfenfluramine or d,l-fenfluramine with a pharmaceutically acceptable inert ingredient.

The invention will now be described through illustrative examples. The examples are not intended to limit the scope of the invention, which limited only by the appended claims.

A subgroup of obese individuals is identified, which individuals describe themselves as being unable to control their eating and who attempt to continue on a weight-reducing diet when experiencing motional distress. These patients are treated for four months by enrolling them in a

weight loss program that includes the administration of dexfenfluramine at 30 mg/day and which involves adherence to a reduced-calorie meal plan. The use of dexfenfluramine is found to enhance the ability of stressed overeaters to lose weight.

Body Mass Index (BMI) is defined as the weight in kilograms of a subject, divided by the subject's height in meters squared.

Applicants conduct a survey of 189 female women of normal body weight (Body Mass Index <25, average Body Mass Index 22.5 ± 0.36), who are not put on the weight-reduction regimen, and 211 obese women (Body Mass Index >25, average Body Mass Index 38.1 ± 0.39). Of these obese women, 50 are entered into the weight loss program. The majority of the obese women responding to the survey report that emotional distress or other types of stress significantly increases their snack intakes and their cravings for sweet and starchy foods. Also, stress clearly decreases their ability to control their food intake and to adhere to a weight-loss regimen. In contrast, the majority of the normal weight women responding to the survey report no alterations in eating behavior when experiencing emotional distress or other stresses. Most obese respondents identify anxiety, depression, exhaustion, boredom, anger, tension and frustration as the stress-induced emotions or symptoms most likely to make them unable to control their food intakes. The kinds of stresses that the patients indicate produce these emotions or symptoms included, among others, family and job problems, boredom, unresolved emotional conflicts and bad news.

Objective measurements of emotional distress are made in some patients using the CES-D (Center for Environmental Studies Depression Form) test, which measures current levels of emotional distress (Radloff and Lenore, *The CES-D Scale: A Self Report Depression Scale for Research in the General Population* Applied Psychological Measurement 1: 385-401, 1977); and the POMS (Profile of Mood States test, that assesses tension, depression, anger and confusion (McNair, D.; Lorr, M. and Droppelman, L.; *Profile of Mood States Manual*;San Diego: Educational and Industrial Testing Service, 1971); both of these references are hereby incorporated by reference. These tests are also given monthly during the treatment period. At the same times, patients also complete questionnaires that ask the patients to rate their appetite and hunger, and also to rate their tendency to eat in response to a variety of emotional and stressful triggers. The patients are also weighed monthly.

The obese, stressed patients receiving dexfenfluramine exhibit a weight loss of 12 ± 1.8 pounds (5.45 ± 0.82 kg) during the four month study period. Six women receiving dexfenflurarnine, whose CES-D scores are above normal at the start of the study, also exhibit a lowered CES-D score. Scores are lowered from 34 to 7, 37 to 8, 22 to 9, 19 to 5, 15 to 7, and 15 to 3, respectively, for these six women. The mean group score, which at the beginning of the study is 9.4, fluctuates between 7 and 8 through the treatment period.

Scores on the appetite and stress-induced overeating scales are also reduced compared with

baseline levels. The initial score on the appetite and hunger scale is 10.5, which decreases to 5.0 during the treatment period. The summed Tension, Depression, Anger and Confusion scores on the POMS test at baseline is 24. This number drops to 16.8 during the study period. Moreover, the score on the emotional triggers to overeating report drops from 23.4 ± 9.8 to 8.6 ± 8.5 standard deviations by the end of the treatment period.

Hence, treatment with a fenfluramine, dexfenfluramine, specifically promotes the ability to control food intake and to lose weight among the stress-induced overeaters. More surprisingly, treatment reduces the indicators of stress in these patients.

In order to confirm the relationship between drugs which enhance serotonin-mediated neurotransmission and the amelioration of symptoms and consequences of stress, i.e. overeating and obesity, a number of serotoninergic drugs are tested on overweight patients using the above protocols.

Specific examples of the results that are obtained with drugs which enhance serotonin-mediated neurotransmission are now provided. The following examples are merely intended to illustrate the invention and are not intended to limit the same.

EXAMPLE I

Example 1 involves treatment with d,l-fenfluramine at 30 mg/day. A preferred dosage is about 5 mg/day to about 150 mg/day.

C.B. is a 48 year old white single female. She states in her screening forms that when she is upset or stressed she snacks on chocolate, popcorn, crackers, pretzels, and candy. She notes that she overeats when feeling frustrated, overwhelmed, and lonely and writes in answer to a question about whether she has difficulty in sticking to a diet when upset or stressed: "In the past when I am not in a formalized program, somehow my brain thinks I'm given a license to graze to placate my emotions when stressed. I tend to break all my own 'house' rules and eat anything I want."

The results are shown in Table 1. Her starting weight is 216 pounds (98.2 kg) and after 4 months on dexfenfluramine, drops to 205.5 pounds (93.4 kg). Her baseline CES-D Mood Scores drop from 5 to 1 over the treatment period, and her emotional triggers decrease from a baseline of 23 to a value of 4 after four months. Hence, the treatment also greatly relieves her emotional distress.

TABLE I

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	5	1	3	2	1
Appetite and Cravings	10	2	5	5	4
Emotional Triggers	23	2	3	2	4

EXAMPLE 2

Example 2 involves treatment with dexfenfluramine hydrochloride at 30 mg/day. A preferred dosage range is from about 15 mg/day to about 45 mg/day.

C.M. is a 46 year old white married physician and mother of two. She reports in her initial screening report that when stressed, she snacks on chocolate, candy, chips, cookies, cake/pie, and popcorn. She writes: "I was on Weight Watchers, doing well even during vacation. But upon the start of the school year with all the schedules to handle, I was unable to keep with the program. Then the Christmas holidays were upon us and I was working really hard at the office. I started gaining weight and I could not stop eating. My appetite has tripled and it is hard for me to say no."

The results are shown in Table 2. Her starting weight is 198 pounds (90.0 kg) and at the end of 4 months on dexfenfluramine, her weight drops to 181.7 pounds (82.6 kg). Her baseline CES-D Mood Scores drop from 19 to 4 over the treatment period, and her emotional triggers decrease from a baseline of 30 to a value of 7 after four months. Hence, the treatment also greatly relieves this patient's stress levels.

TABLE 2

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	19	5	2	3	4
Appetite and Cravings	9	6	8	3	5
Emotional Triggers	30	12	13	5	7

EXAMPLE 3

Example 3 involves the treatment of a 57 year old married female with lithium carbonate at 900 mg/day for four months. A preferred dose is about 600 mg/day to about 1500 mg/day.

D.R. states in her screening forms that when she is upset or stressed she overeats on beer and crabs, as well as snack food such as potato chips and peanuts. This occurs when she feels stress or frustration from her employment as a government lawyer.

The results are shown in Table 3. Her starting weight is 246 pounds (111.8 kg) and after 4 months on lithium drops to 225 pounds (102.3 kg). Her baseline CES-D Mood Scores drop from 4 to 2 over the treatment period, and her emotional triggers decrease from a baseline of 15 to a value of 7 after four months. Hence, the treatment also greatly relieves her emotional distress and stress.

TABLE 3

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	4	3	3	2	2
Appetite and Cravings	14	6	9	5	3
Emotional Triggers	15	16	10	6	7

EXAMPLE 4

Example 4 involves the treatment of a 35 year old single white female with fluoxetine hydrochloride at a dose from 20 mg/day for the first two weeks, 40 mg/day the second two weeks, 60 mg/day the third two weeks, and 80 mg/day through the end of the four month trial. The preferred dose is about 10 mg/day to about 160 mg/day.

The results are shown in Table 4. T.M. reports in her initial screening report that when stressed, she chronically overeats at meals, although she eats nothing between and after meals. Her overeating takes the form of non-stop eating, consuming a loaf of bread and a stick of butter at a single meal. Her starting weight is 183 pounds (83.2 kg) and at the end of 4 months on fluoxetine hydrochloride, her weight drops to 172 pounds (78.2 kg). Her baseline CES-D Mood Scores drop from 15 to 7 over the treatment period, and her emotional triggers decrease from a baseline of 31 to a value of 12 after four months. Hence, the treatment also greatly relieves this patient's stress levels.

TABLE 4

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	15	10	2	6	7
Appetite and Cravings	17	6	9	3	4
Emotional Triggers	31	22	13	10	12

EXAMPLE 5

Example 5 involves the treatment of a 76 year old single white female with fluvoxamine maleate at a dose from 50 mg/day for the first week, 100 mg/day the second week, and 150 mg/day through the end of the four month trial. The preferred dose is about 25 mg/day to about 300 mg/day.

J.B. complains of feelings of stress associated with social activities in the retirement community in which she lives. While clearly overweight, she does not complain about weight nor apparently recognizes her condition.

The results are shown in Table 5. Her starting weight is 302 pounds (137.3 kg) and after 4 months on dexfenfluramine, drops to 286 pounds (130 kg). Her baseline CES-D Mood Scores drop

from 23 to 17 over the treatment period, and her emotional triggers decrease from a baseline of 34 to a value of 24 after four months. The treatment relieves her social stress and has the additional benefit of modest weight reduction.

TABLE 5

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	23	26	16	15	17
Appetite and Cravings	18	16	11	12	14
Emotional Triggers	34	27	30	20	24

EXAMPLE 6

Example 6 involves the treatment of a 42 year old married white female with sertraline hydrochloride at a dose from 50 mg/day for the first week, 100 mg/day the second week, and 200 mg/day through the end of the four month trial. The preferred dose is about 25 mg/day to about 400 mg/day.

P.Q. is employed as an accountant, has two small children, and experiences stress during the tax season. She eats between meals and reports wakening at night with anxiety which is relieved by consumption of ice cream.

The results are shown in Table 6. Her starting weight is 173 pounds (78.6 kg) and at the end of 4 months on sertraline, her weight drops to 160 pounds (72.7 kg). Her baseline CES-D Mood Scores drop from 20 to 12 over the treatment period, and her emotional triggers decrease from a baseline of 22 to a value of 3 after four months. Hence, the treatment relieves both the stress levels and the overweight.

TABLE 6

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	20	16	16	10	12
Appetite and Cravings	15	12	5	3	1
Emotional Triggers	22	12	13	5	3

EXAMPLE 7

Example 7 involves the treatment of a 38 year old single white female with venlafaxine hydrochloride at a dose from 75 mg/day for the first week, 100 mg/day the second week, and 150 mg/day through the end of the four month trial. The preferred dose is about 50 mg/day to about 300 mg/day.

L.Z., a single mother of four children, operates a day care center in her home and complains of continual stress. She eats baked goods excessively in the evening after the children have gone home or to bed.

The results are shown in Table 7. Her starting weight is 184 pounds (83.6 kg) and after 4 months on dexfenfluramine, drops to 169 pounds (76.8 kg). Her baseline CES-D Mood Scores drop from 8 to 2 over the treatment period, and her emotional triggers decrease from a baseline of 14 to a value of 2 after four months. Hence, the treatment also greatly relieves her emotional distress.

TABLE 7

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	8	4	6	2	2
Appetite and Cravings	10	6	7	3	1
Emotional Triggers	14	9	4	6	2

EXAMPLE 8

Example 8 involves the treatment of a 44 year old single white female with amitriptyline hydrochloride at a dose from 75 mg/day for the first week, to 100 mg/day through the end of the four month trial. The preferred dose is about 50 mg/day to about 200 mg/day.

E.E. reports stress from her employment as a dispatcher for a trucking company. Her discomfort is relieved by eating fried foods, especially fried potatoes.

The results are shown in Table 8. Her starting weight is pounds (90.0 kg) and at the end of 4 months on dexfenfluramine, her weight drops to pounds (82.6 kg). Her baseline CES-D Mood Scores drop from 29 to 18 over the treatment period, and her emotional triggers decrease from a baseline of 25 to a value of 3 after four months. Hence, the treatment also greatly relieves this patient's stress levels.

TABLE 8

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	29	22	20	23	18
Appetite and Cravings	19	16	8	13	8
Emotional Triggers	25	22	13	5	3

EXAMPLE 9

Example 9 involves the treatment of a 30 year old married white female with trazodone hydrochloride at a dose of 100 mg/day in divided doses of 50 mg each through the end of the four month trial. The preferred dose is about 50 mg/day to about 200 mg/day.

N.J. , with three small children, reports an unhappy and stressful home life with an interfering mother-in-law and ineffectual husband. Her stress seems relieved by lite-night snacking on sweet food.

The results are shown in Table 9. Her starting weight is 203 pounds (92.3 kg) and at the end of 4 months on sertraline, her weight drops to 160 pounds (72.7 kg). Her baseline CES-D Mood Scores drop from 9 to 1 over the treatment period, and her emotional triggers decrease from a baseline of 12 to a value of 3 after four months. Hence, the treatment relieves both the stress levels and the overweight.

TABLE 9

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	9	16	16	10	1
Appetite and Cravings	9	5	5	3	5
Emotional Triggers	12	12	9	5	3

EXAMPLE 10

Example 10 involves the treatment of a 31 year old married white female with imipramine hydrochloride at an intramuscular dose of 75 mg/day through the end of the four month trial. The preferred dose is about 50 mg/day to about 150 mg/day.

A.R., is employed at a consulting engineering firm and attends law school at night. Her regimented schedule and lack of exercise may contribute to her feelings of stress, which engenders over-eating.

The results are shown in Table 10. Her starting weight is 163 pounds (74.1 kg) and after 4 months on imipramine, drops to 155 pounds (70.4 kg). Her baseline CES-D Mood Scores drop from 36 to 20 over the treatment period, and her emotional triggers decrease from a baseline of 22 to a value of 8 after four months. Hence, the treatment also greatly relieves her emotional distress.

TABLE 10

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	36	34	26	21	20
Appetite and Cravings	15	12	7	3	6
Emotional Triggers	22	15	14	6	8

EXAMPLE 11

Example 11 involves the treatment of a married 42 year old white female with trimipramine maleate at a dose from 75 mg/day for the first week, to 100 mg/day through the end of the four month trial. The preferred dose is about 50 mg/day to about 200 mg/day.

A.B., a teacher in a metropolitan school, reports stress which she attributes to her work and generally unhappy home life. She is unable to control episodic binge eating of ice cream and cake.

The results are shown in Table 11. Her starting weight is 180 pounds (81.8 kg) and at the end of 4 months on trimipramine, her weight drops to 158 pounds (71.8 kg). Her baseline CES-D Mood Scores drop from 25 to 13 over the treatment period, and her emotional triggers decrease from a baseline of 14 to a value of 3 after four months. Hence, the treatment also greatly relieves this patient's stress levels.

TABLE 11

	Bas line	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	25	22	20	15	13
Appetite and Cravings	11	9	8	13	6
Emotional Triggers	14	8	13	6	3

EXAMPLE 12

Example 12 involves the treatment of a single 50 year old white female with phenelzine sulfate at a dose from 45 mg/day for the first week, to 60 mg/day through the end of the four month trial, each daily dose taken in three portions. The preferred dose is about 15 mg/day to about 120 mg/day.

D.C. is a suburban bus driver and finds driving in traffic stressful. She constantly diets but is unable to successfully lose weight.

The results are shown in Table 12. Her starting weight is 184 pounds (83.6 kg) and at the end of 4 months on phenelzine, her weight drops to 174 pounds (79.1 kg). Her baseline CES-D Mood Scores drop from 20 to 14 over the treatment period, and her emotional triggers decrease from a baseline of 20 to a value of 7 after four months. Hence, the treatment also greatly relieves this patient's stress levels.

TABLE 12

	Baseline	Month 1	Month 2	Month 3	Month 4
Mood Scores CES-D	20	22	20	15	14
Appetite and Cravings	19	15	8	13	12
Emotional Triggers	20	8	13	6	7

EXAMPLE 13

The effect of the hydrochloride salt of 6-Chloro-2-(1-piperazinyl)pyrazine (MK-212, which is obtained from Merck & Co., Inc. Whitehouse Station, NJ, on stress related eating in animals is determined through the observation of the effect of experimental compounds on stress-related eating in adult Sprague-Dawley rats. These rats are widely used as a recognized animal model useful in predicting the effect of serotoninergic drugs in humans.

In these experiments, a group of 5 adult female and 5 adult male Sprague-Dawley rats weighing between 200 and 250 grams each are used as control animals. An untightened clamp is placed on the tail of these animals. The untightened clamp provides the unstressed condition. Each animal is placed in an individual cage and allowed free access to food. The amount of food consumed is determined at 2, 4 and 8 hours after the initiation of the trial. A similar group of rats has a clamp tightened on the tail. The amount of food consumed by this stressed group of rats is shown in the 0 mg/kg column. Three similar groups of stressed rats are injected with 1, 2, 5, or 10 mg/kg body weight of MK-212 one hour before initiation of the experiment.

The results are shown in Table 13. The average amount of food in mg which is consumed per rat 8 hours after initiation of the trials is shown in the following table. The relative amounts of stress eating with the amount at 0 mg/kg MK-212 as 100% is also shown in the Stress Eating row. The preferred daily dose of MK-212 is about 1 mg/kg body weight to about 10 mg/kg body weight.

Table 13 shows MK-212 reduces stress-related eating which indicates MK-212 reduces stress.

TABLE 13

MK-212	0 mg/kg	1 mg/kg	2 mg/kg	5 mg/kg	10 mg/kg
Control Rats	1.25	1.32	1.20	1.16	1.03
Stressed Rats	4.63	4.14	3.78	2.01	.97
Stress Eating	3.38 (100%)	2.82 (83%)	2.58 (76%)	0.85 (25%)	0.0 (0%)

EXAMPLE 14

Example 14 shows the effect of (S)-2-(4, 4, 7-trimethyl-1, 4-dihydro-indol (1, 2-B) pyrrol-1-yl-1-methylethylamine (Ro 60-175/ORG 35030) which is obtained from F. Hoffmann-LaRoche Ltd., Basel, Switzerland, on stress-induced eating. The experiment is done as in Example 13 and Table 13 except that Ro 60-175/ORG 35030 is used instead of MK-212. The preferred daily dose of Ro 60-175/ORG 35030 is about 1 mg/kg body weight to about 10 mg/kg body weight.

Table 14 shows that Ro 60-175/ORG 35030 reduces stress related eating which indicates Ro 60-175/ORG 35030 reduces stress.

TABLE 14

Ro 60-175/ORG 35030	0 mg/kg	1 mg/kg	2 mg/kg	5 mg/kg	10 mg/kg
Control Rats	1.31	1.28	1.30	1.20	1.13
Stressed Rats	4.51	3.66	1.43	1.30	1.16
Stress Eating	3.20 (100%)	2.38 (74%)	0.13 (4%)	0.10 (3%)	0.03 (1%)

EXAMPLE 15

The effect of (S)-2-(Chloro-5-fluoro-indol-1-yl)-1-methylethylamine (Ro 60-0332/ORG 35035) which is obtained from F. Hoffmann LaRoche Ltd., Basel, Switzerland, on eating in stressed rats is determined as in EXAMPLE 13 and Table 13, except Ro 60-0332/ORG 35035 is used rather than MK-212. The preferred daily dose of Ro 60-0332/ORG 35035 is about 1 mg/kg body weight to about 10 mg/kg body weight.

Table 15 shows that Ro 60-0332/ORG 35035 reduces stress-related eating which indicates Ro 60-0332/ORG 35035 reduces stress.

TABLE 15

Ro 60-0332/ORG 35035	0 mg/kg	1 mg/kg	2 mg/kg	5 mg/kg	10 mg/kg
Control Rats	1.23	1.29	1.20	1.21	1.28
Stressed Rats	4.72	4.87	2.19	1.83	1.74
Stress Eating	3.49 (100%)	3.58 (103%)	0.99 (28%)	0.60 (17%)	0.46 (13%)

While the invention has been described herein with reference to specific and preferred embodiments, it is understood that changes, modifications, substitutions and omissions may be made without departing from the spirit and scope of the invention, which is limited only by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating a human subject exhibiting one or more symptoms of stress, which comprises administering to said subject an effective amount of a compound which enhances serotonin-mediated neurotransmission, or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the compound which enhances serotonin-mediated neurotransmission or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 5 mg/day to about 150 mg/day.

3. A method of treating a human subject exhibiting one or more symptoms of stress, which comprises administering to said subject an effective amount of a compound selected from the group of compounds consisting of d,l-fenfluramine, dexfenfluramine, tryptophan, lithium, chlorimipramine, cyanimipramine, fluoxetine, paroxetine, fluvoxamine, citalopram, femoxitine, cianopramine, sertraline, sibutramine, venlafaxine, ORG 6582, RU 25591, LM 5008, DU 24565, indalpine, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone, amitriptyline, imipramine, trimipramine, doxepin, protriptyline, nortriptyline, dibenzoxazepine, deprenyl, isocarboxazide, phenelzine, tranylcypromine, furazolidone, procarbazine, moclobemide, brofaromine, nefazodone, bupropion, MK-212, DOI, m-CPP, Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, α-methyl-5-HT, TFMPP, bufotenin, Ru 24969, quipazine, 5-carboxyamidotryptamine, sumatriptan, CGS 12066, 8-OH-DPAT, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, SB 206553, and pharmaceutically acceptable salts thereof.

4. The method of claim 3 wherein the compound that enhances serotonin-mediated neurotransmission or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 5 mg/day to about 1500 mg/day.

5. A method of treating a human subject exhibiting one or more symptoms of stress, which comprises administering to said subject an effective amount of d,lfenfluramine, dexfenfluramine, or a pharmaceutically acceptable salt thereof.

6. The method of claim 5 which comprises administering an effective amount of d,l-fenfluramine or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 in which said d,l-fenfluramine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 15 to about 150 mg/day.

8. The method of claim 6 in which said d,l-fenfluramine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 40 to about 80 mg/day.

9. The method of claim 5 which comprises administering an effective amount of dexfenfluramine or a pharmaceutically acceptable salt thereof.

10. The method of claim 9 in which said dexfenfluramine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 5 to about 150 mg/day.

11. The method of claim 9 in which said dexfenfluramine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 15 to about 45 mg/day.

12. The method of claim 3 which comprises administering an effective amount of lithium or a pharmaceutically acceptable salt thereof.

13. The method of claim 12 in which said lithium or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 600 mg/day to about 1500 mg/day.

14. The method of claim 3 which comprises administering an effective amount of fluoxetine or a pharmaceutically acceptable salt thereof.

15. The method of claim 14 in which said fluoxetine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 10 mg/day to about 160 mg/day.

16. The method of claim 3 which comprises administering an effective amount of fluvoxamine or a pharmaceutically acceptable salt thereof.

17. The method of claim 16 in which said fluvoxamine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 25 mg/day to about 300 mg/day.

18. The method of claim 3 which comprises administering an effective amount of sertraline or a pharmaceutically acceptable salt thereof.

19. The method of claim 18 in which said sertraline or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 25 mg/day to about 400 mg/day.

20. The method of claim 3 which comprises administering an effective amount of venlafaxine or a pharmaceutically acceptable salt thereof.

21. The method of claim 20 in which said venlafaxine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 50 mg/day to about 300 mg/day.

22. The method of claim 3 which comprises administering an effective amount of amitriptyline or a pharmaceutically acceptable salt thereof.

23. The method of claim 22 in which said amitriptyline or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 50 mg/day to about 200 mg/day.

24. The method of claim 3 which comprises administering an effective amount of trazodone or a pharmaceutically acceptable salt thereof.

25. The method of claim 24 in which said trazodone or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 50 mg/day to about 200 mg/day.

26. The method of claim 3 which comprises administering an effective amount of imipramine or a pharmaceutically acceptable salt thereof.

27. The method of claim 26 in which said imipramine or a pharmaceutically acceptable

salt thereof is administered at a dose ranging from about 50 mg/day to ab ut 150 mg/day.

28. The method of claim 3 which comprises administering an effective amount of trimipramine or a pharmaceutically acceptable salt thereof.

29. The method of claim 28 in which said trimipramine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 50 mg/day to about 200 mg/day.

30. The method of claim 3 which comprises administering an effective amount of phenelzine or a pharmaceutically acceptable salt thereof.

31. The method of claim 30 in which said phenelzine or a pharmaceutically acceptable salt thereof is administered at a dose ranging from about 15 mg/day to about 120 mg/day.

32. The method of claim 1 wherein the compound which enhances serotonin-mediated neurotransmission is a compound which activates postsynaptic serotonin receptors.

33. The method of claim 32 wherein the compound which activates postsynaptic serotonin receptors is selected from the group of compounds consisting of MK-212, DOI, m-CPP, Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035, Ro 60-0175, Org 12962, Ro 60-0332, (S)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine 1:1 C4H4O4, (S)-2-(4,4,7-trimethyl-1,4-dihydro-indeno(1, 2-b)pyrrol-1-yl)-1-methylethylamine 1:1 C4H4O4, and SB 206553.

34. The method of claim 33 which comprises administering an effective amount of MK-212 or a pharmaceutically acceptable salt thereof.

35. The method of claim 34 wherein said MK-212 or a pharmaceutically acceptable salt thereof is administered at a daily dose ranging from about 0.1 mg/kg body weight to about 10.0 mg/kg body weight.

36. The method of claim 33 which comprises administering an effective amount of Ro 60-175/ORG 35030 or a pharmaceutically acceptable salt thereof.

37. The method of claim 36 wherein said Ro 60-175/ORG 35030 or a pharmaceutically acceptable salt thereof is administered at a daily dose ranging from about 0.1 mg/kg body weight to about 10.0 mg/kg body weight.

38. The method of claim 33 which comprises administering an effective amount of Ro 60-0332/ORG 35035 or a pharmaceutically acceptable salt thereof.

39. The method of claim 38 wherein said Ro 60-0332/ORG 35035 or a pharmaceutically acceptable salt thereof is administered at a daily dose ranging from about 0.1 mg/kg body weight to about 10.0 mg/kg body weight.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16153

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/135, 31/415, 31/495; AOIN 43/60
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/651, 397, 252, 255, 247, 256, 303, 319, 357, 359, 428, 429, 647, 657

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,283,263 A (NORDEN) 01 February 1994, see entire document.	1-39
X	US 5,561,149 A (AZRIA et al) 01 October 1996, see entire document.	1-39
X	US 5,597,826 A (HOWARD et al) 28 January 1997, see entire document.	1-39
X, P	US 5,852,020 A (MARCUS et al) 22 December 1998, see entire document.	1-39
X, P	US 5,916,923 (RUDOLPH et al) 29 June 1999, see entire document.	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER:
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514/651, 397, 252, 255, 247, 256, 303, 319, 357, 359, 428, 429, 647, 657